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15. SUBJECT TERMS

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INTRODUCTION: Combat veterans who have sustained a traumatic brain injury (TBI) can show impairments in behavioral and cognitive control and increases in impulsivity. In addition, many with mild TBI will also have post-traumatic stress disorder (PTSD). To improve diagnostic capabilities and better define treatment alternatives, it is important to determine the unique (and shared) contributions of each disorder to deficits in cognitive function and emotional control. Three specific control functions are being targeted: (1) **resolving conflict** between competing responses and competing aspects of a visual display; (2) **monitoring for errors** in performance and adjusting behavior accordingly; (3) **multi-tasking**, or the ability to maintain adequate performance in dual task situations. Converging evidence is obtained through the combined use of behavioral testing, electrophysiological recording (event-related potentials, ERPs), and structural imaging (diffusion tensor imaging, DTI). The project applies innovative methods by expanding the application of ERPs into the cognitive and behavioral domains most troublesome for patients with TBI and PTSD.

<u>BODY</u>: In the third year of the project, we enrolled 6 patients (total n=36) and 12 demographically-matched military control subjects (total n=30) and tested them on the first in a series of computer-based experiments that evaluate reaction time, cognitive processing, and emotional reactivity. In addition, we collected self-report information from 3 questionnaires. We have also tested 14 more civilian control participants (total n=26) to serve as another comparison group. We also collected data from 28 subjects in a second series of computerized experiments (total n=52). Finally, we continued recording EEG data in Exp. 2 and Exp. 4. The research accomplishments associated with each task outlined in the approved Statement of Work are summarized below.

Project Timeline and Milestones					
		Year 1	Year 2	Year 3	
Patient Recruitment		ongoing	ongoing	ongoing	
	Matched Controls	4	14	12	
	TBI only	1	1	0	
	PTSD only	6	2	0	
	TBI + PTSD	11	9	6	
Pilot Studies		Exp. 1-2	Exp. 4	Exp. 4	
Behavioral Testing		Exp. 1	Exp. 1	Exp. 1	
ERPs			Exp. 2	Exps. 2, 4	

Phase 1: Patient Recruitment: We enrolled 6 additional patients (all Veterans) into the study during the third year of the project. Of these, all had suffered one or more mild TBIs or probable TBIs (i.e., concussions) based on standard criteria from, e.g., the American Congress of Rehabilitative Medicine (ACRM, 1993) and WHO (Von Holst & Cassidy, 2004), as accepted by the VA and the DoD (see http://www.pdhealth.mil/TBI.asp). All of the 6 Veterans enrolled in the project this year had received a PTSD diagnosis as well. Thus, of the three originally proposed patient groups, there are now a total of 26 in the TBI+PTSD group, 8 with PTSD only, and 2 with TBI only.

We have been unsuccessful in recruiting a cohort of mTBI patients without PTSD. This is an issue that affects all investigators working with similar groups of OIF/OEF Veterans. The concern is whether an adequate sample of Veterans with mild TBI only, with no PTSD, can be

found. In our experience over three years, most of the patients who meet the selection criteria for mild TBI (mTBI) also have a formal PTSD diagnosis. Due to the difficulty of finding patients with "pure" mTBI in isolation from PTSD, we will not focus on including this group in the current project. In our experience, these individuals may show better recovery from post-concussive symptoms (PCS) and hence do not show up at neurology or mental health clinics, and may not even be receiving health care from the VA.

In addition to the patients, we have recruited 12 more demographically matched controls (Veterans, mean age = 34). Our concerted effort to recruit a greater number of Veteran control participants has been successful. Finally, subjects completed three standardized questionnaires: the Barratt Impulsiveness Scale (BIS), the PTSD Checklist – Military (PCL-M), and the Beck Depression Inventory (BDI).

Phase 2: Pilot Studies:

Allocation of Attention: As part of our regular EEG protocol, all subjects performed a brief auditory "oddball" task. A typical oddball task contains many frequent or **standard** trials and an occasional infrequent **target** that requires a response. The infrequent target elicits a large positive ERP waveform over the central-parietal brain regions, commonly referred to as the P300 or P3b. The P3b is thought to reflect attention-driven processes that evaluate features about the current stimulus and update working memory accordingly (Polich, 2007). In some cases, a third stimulus type is also included in an oddball task: a **novel** non-target stimulus. No behavioral response is required to the novel stimulus, which elicits the P3a component over frontal brain regions (Knight, 1984). Previous work has demonstrated that PTSD patients show an enhanced P3a response to novel stimuli in the three-stimulus auditory oddball (Kimble et al., 2000). This is consistent with the theory that PTSD patients are more affected by distracting, unusual stimuli, which may lead to difficulties in concentration. Based on the existing literature, we predicted that participants with PTSD would show an enhanced P3a novelty effect.

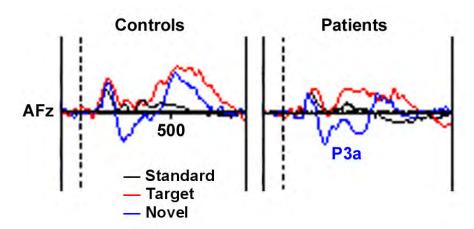


Fig. 1 – Averaged ERPs from controls (n=11) and patients with both PTSD and mTBI (n=11) in the auditory oddball task. The standard stimulus was a 1000 Hz tone, the target a 1200 Hz tone, and the novels were unique sound effects (e.g., car horn, waterfall, machine noises) that did not repeat from trial to trial. The midline anterior frontal electrode (AFz) highlights the P3a component (in blue). Negative polarity is plotted upwards, stimulus onset occurred at the zero line.

Preliminary results from 11 controls and 11 patients with both PTSD and mild TBI are shown in Fig. 1. As predicted, the patient group showed an increase in the overall mean amplitude of the

P3a, consistent with their PTSD diagnosis. The patients also showed a delay in the peak latency of the P3a component, suggesting it took them longer to fully evaluate the novel stimuli.

<u>Support Vector Machine Classification</u>: One of the goals of examining neural activity in patients with mTBI and PTSD is to gain a better understanding of the cognitive deficits seen in individuals with these disorders. These characterizations might also make it possible, using only electrophysiological data, to classify individuals as either having the disorder or as not having indicators of the disorder. This has the possibility of aiding health care professionals in assessing the extent and nature of the damage caused by one or more disorders. One way of doing this is through machine learning.

Support vector machines (SVMs) are supervised learning methods used for classification, regression, novelty detection, and pattern recognition. The underlying feature of an SVM is the construction of a hyperplane that divides data vectors into two sets. This hyperplane is defined by inner products of training data vectors that have been projected to a higher dimension space. This is a successful approach because the linear dependencies introduced by the additional dimensionality often make the division easier. Also, because the approach employs inner products of the data projections and not the projections themselves, it typically entails a lighter computational effort (Karatzoglou et al., 2006).

Devin Adair, an accomplished student who received a research fellowship for an undergraduate thesis project, began to apply this type of analysis to the novelty P3a data (Adair, 2011). The data were filtered from 2-30 Hz and the area under the curve was measured from 250 to 300 msec. SVM analysis was done in R using C-Classification. Although the results are extremely preliminary at this point, classification of groups resulted in above chance (50%) mean classification for each group (mTBI/PTSD and Military Controls) and overall percent correct for the P3a (% Correct=64.19, p<0.0001; mTBI/PTSD %=61.2, p<0.0001; Military Control %=66.86, p<0.0001; Fig. x).

We realize these percentages are not very impressive yet, but improvements to the signal/noise ratio, an increase in the number of subjects, and inclusion of more variables in the model may help in the future to improve the % correct classification based on EEG measures.

<u>Phase 3: Behavioral Testing:</u> Testing and data analysis in the emotional Stroop task (Exp. 1) are ongoing and will be completed within the next quarter. The Go/NoGo task is another executive control task that provides a measure of response inhibition, and a paper describing those findings will be submitted for publication in the next quarter as well. Results from these studies are summarized below.

Experiment 1 – Emotional Stroop task with Combat-Related Words: This experiment was designed to be an objective behavioral measure that may be able to distinguish between combat Veterans with a PTSD diagnosis and those without. It is a variant of the color word Stroop task, in which participants name the font color of words presented on the screen while ignoring the words themselves. In our current paradigm, the words are presented in blocks of negative emotional words, positive emotional words, combat-related words, and appropriately matched neutral words. The metrics of interest are reaction times (RTs) for naming the color of combat words relative to neutral words, as the former are thought to divert attention away from the

primary task in OEF/OIF Veterans with PTSD. The critical stimulus list included combat-related words such as FALLUJA, KANDAHAR, MARTYR, and IED.

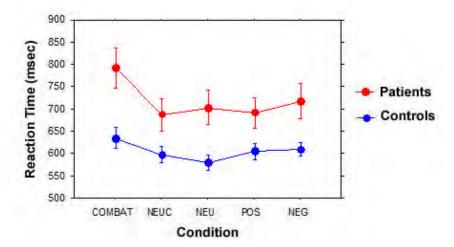


Fig. 2 – Color naming reaction times (RTs) for the five different stimulus conditions: com = combat-related words; neuc = neutral words matched to combat; neu = neutral words matched to negative words; pos = positive emotional words; neg = negative emotional words.

Relative to the military control group, the patients showed slower RTs across all stimulus conditions (Fig. 2). Furthermore, condition interacted with group. The most important comparison is the emotional Stroop effect (slowing of RTs) for combat-related words relative to neutral words (Fig. 3). Here, the effect in the patient group (104 msec) is nearly three times as large as that seen in the military control participants (37 msec). Pairwise comparisons of combat-related words vs. neutral words revealed a highly significant effect for the patients (p<.0001), but less so in control subjects (p<.04).

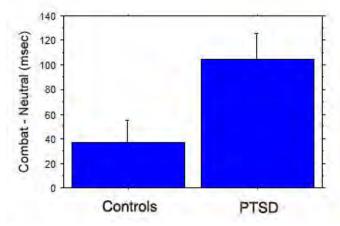


Fig. 3 – The combat Stroop effect: color naming RTs for combat-related words minus RTs for neutral words (in milliseconds) for the Veteran controls (Left) and the patients (Right).

With the increased number of subjects in this reporting period, there were significant correlations between the size of the combat Stroop effect and scores on the PTSD Checklist – Military (PCL-M) and the Beck Depression Inventory (BDI). Of the three PTSD symptom clusters (reexperiencing, avoidance/numbing, hyperarousal), the greatest correlation was with the reexperiencing subscale across both groups (Spearman's rho=.45, p=.001). The emotional Stroop

task shows promise as an objective measure of PTSD symptomology suitable for use as an outcome measure in PTSD intervention studies (Ashley et al., 2011).

<u>Go/NoGo Task – Motor Response Inhibition:</u>

This task measures a person's ability to inhibit an inappropriate response, a key function attributed to the frontal lobes and a major component of executive control (Miyake et al., 2000). Single letters were rapidly presented on a computer screen, and subjects were instructed to respond as quickly as possible to any letter except "X," the NoGo stimulus. The difficulty of the task was manipulated by altering the probability of "Go" trials relative to "NoGo" trials, i.e., 50% Go trials vs. 90% Go trials (with 50% NoGo vs. 10% NoGo, respectively). Performance measures (error rates and reaction times) from the patient group (n=36) were compared to those from an age-matched Veteran control group (n=30). All participants made more errors on the difficult condition (p<.0001), when the need to inhibit responses was rare (Fig. 4). The patients were significantly impaired on this task overall, committing more errors in both conditions (p<.0001). Furthermore, "Go" probability interacted with group (p<.003). RTs did not differ between the groups (p's>.4), suggesting that a speed-accuracy trade-off in the patients cannot account for their deficit.

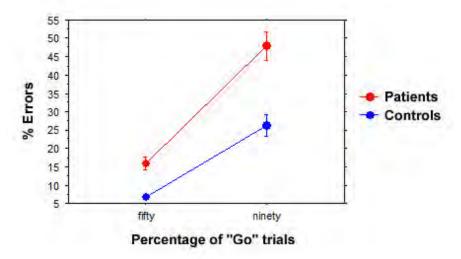


Fig. 4 – Percentage of errors on the GoNoGo task for both conditions (which were presented in separate blocks). The "fifty" condition means that "Go" trials requiring a button press response occurred on 50% of the trials, and the "ninety" condition means that "Go" trials occurred on 90% of the trials.

Veterans with TBI+PTSD did not make more mistakes on this task than Veterans with PTSD only, suggesting that additional mTBI did not compound the response inhibition deficit associated with PTSD. There were only two patients with mild TBI without PTSD in our patient pool. However, Nelson and colleagues (2009) found that OEF/OIF Veterans with mTBI+PTSD performed worse than those with mTBI without PTSD on speed of processing and executive function tasks.

Self-rated impulsivity on the Barratt Impulsiveness Scale (BIS) showed a modest correlation with performance in the 90% Go condition, when responses were harder to inhibit (p<.03). Errors in this condition did not correlate at all with the motor subscale of the BIS, which was expected to be most relevant for the Go/NoGo task. Although this questionnaire is one of the most commonly used measures of impulsivity (Spinella, 2007), it has not yet been validated in

participants with mild TBI and PTSD. In addition, a recent study suggests that neurocognitive measures may not correlate with the BIS (Wu et al., 2009).

Instead, scores on the BDI and PCL-M showed a much better correlation with performance: more severe levels of depression (Spearman's rho=.49, p<.0001) and PTSD symptoms (rho=.49, p<.0001) were both associated with higher error rates in the 90% Go condition. Finally, the striking correlation between PCL-M and BDI scores was notable (rho=.87, p<.0001), indicating that PTSD and depression showed a high level of co-morbidity in these OEF/OIF Veterans.

Interestingly, previous GoNoGo results in TBI patients have been mixed. Some papers have reported deficits (Robertson et al., 1997), while others have not (Whyte et al., 2006). We recently reported that a group of moderate to severe TBI patients with lesions to orbitofrontal cortex were not impaired in this task (Swick et al., 2008). On the other hand, civilians with PTSD (and no TBI) showed an increased error rate and reduced recruitment of frontal cortical regions in a neuroimaging study of response inhibition (Falconer et al., 2008). Taken together, these results suggest that PTSD symptoms interfere with effective response inhibition. Our prior work demonstrated that stroke patients with focal lesions in the left inferior frontal gyrus showed a pattern of impairment similar to that reported here (Swick et al., 2008). However, the present group of OIF/OEF Veterans had an even greater deficit in motor response inhibition, which can have important implications for daily life. Thus, the Go/NoGo task provides a measure of inhibitory control that is more objective than self-reported evaluations of behavioral tendencies.

<u>Stop-Signal Reaction Time Task – Motor Response Inhibition:</u>

The Stop-Signal Task (SST) also measures a person's ability to inhibit an inappropriate response, much like the Go/NoGo task described in the prior section. In the SST, responses are made on every trial unless a Stop Signal (e.g., a tone) is presented (Logan et al., 1997). The interval between the Go stimulus and the Stop stimulus (stop-signal delay) is varied using an adaptive procedure designed to produce a 50% error rate (Verbruggen & Logan, 2008). Performance is modeled as a "race" between Go and Stop processes, and the stop-signal reaction time ("stopping time") is calculated as a measure of inhibitory control.

We implemented a standard version of the task where left and right arrows are presented on the screen, each requiring a left or right key press response **unless** a tone is presented (25% of the trials). We currently have data from 16 patients and 17 veteran controls (Fig. 5). Statistical results indicated that although there was a trend for the patients to show longer stopping times (slower Stop Signal RTs), this was not significant (p=.24). Some investigators tout this task as a better measure of response inhibition than GNG, but others have pointed out that the Stop Signal task is subject to strategic and motivational influences (Leotti & Wager, 2010). Thus, it may not be a "pure" measure of inhibitory control abilities. Our findings are in agreement with this view.

The intact SST performance in the patients is in contrast to the impaired performance of these same participants in the Go/NoGo task. A previous meta-analysis of the neuroimaging literature indicated that SST and GNG have both overlapping and distinct neural substrates, the latter reflected by differential recruitment of two cognitive control networks (Swick et al., 2011a). To see whether performance on the two tasks was correlated, we tested a larger group of subjects (including the ones presented in Fig. 4). Results demonstrated that NoGo errors were not

correlated with SSRT (Swick et al., 2011b). Combined with the meta-analysis results, these data suggest GNG and SST are not identical measures of response inhibition.

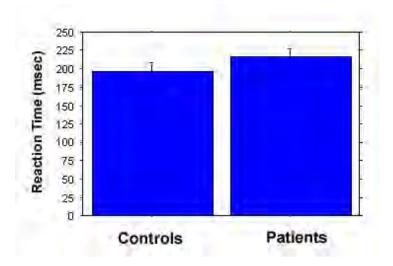


Fig. 5 – Results from the Stop-Signal reaction time task, showing stopping time (in milliseconds). The Stop-Signal RT is purportedly a measure of the time required to cancel a movement that is already planned. More efficient stopping ability is represented by **shorter** SSRTs.

Although the two tasks are often treated interchangeably (Lenartowicz et al., 2010), it is unclear whether they tap the same cognitive processes and neural substrates. This is important because assertions that the NoGo vs. Go and Stop vs. Go comparisons are both measuring the same cognitive construct ("Suppression of actions that are inappropriate in a given context and that interfere with goal-driven behavior") have theoretical and practical implications. From a theoretical perspective, new efforts to develop formal ontologies of cognitive control functions rely on observable indicators, i.e. behavioral performance and brain activation measures obtained from specific tasks (Lenartowicz et al., 2010). Presumably, if GNG and SSRT activate non-overlapping brain regions, then they reflect the engagement of different processes to some degree. From a practical standpoint, impaired performance on either of these tasks in patient populations is often taken as an indication of specific prefrontal cortex abnormalities (Clark et al., 2007) or frontal lobe dysfunction more generally (Barkley et al., 1992; van der Schoot et al., 2000). Defining the behavioral details and neural substrates of impulse control problems is an important goal for developing treatment strategies for the OEF/OIF population.

Phase 4: ERP Studies:

EEG data collection and analysis in Experiments 2 and 4 are ongoing. Our most exciting result is a significant group difference in the error-related negativity component (ERN). The ERN is generated when subjects make errors in speeded reaction time tasks (Gehring et al., 1993). This measure is considered to be an on-line index of performance monitoring that reflects neural activity in the medial prefrontal cortex. Lesion evidence suggests that a major generator of this component is located in dorsal anterior cingulate cortex (Swick & Turken, 2002).

The plot below shows the averaged event-related potentials (ERPs) from 11 control participants and 11 patients with mTBI/PTSD to correct responses vs. errors in a difficult dual task flanker

interference paradigm (Pratt et al., in press). The amplitude of the ERN was significantly larger in controls (-5.6 μ V) than in the patient group (-2.7 μ V).

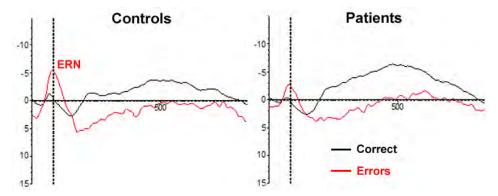


Fig. 6 – The ERN component recorded from 11 Control Veterans and 11 Veterans with mTBI/PTSD in the dual task flanker. These ERPs (from the central midline electrode Cz) were time-locked to response onset (shortly before the marker, approximately 50 ms before the response). Congruent trials are in black, incongruent trials are in red. Negative is plotted upwards. ERN amplitude is significantly reduced in the patients.

This is the first ever demonstration that individuals with PTSD have a reduction in ERN amplitude. The size of the ERN correlated significantly with scores on the PCL-M, such that more severe symptoms were associated with a smaller ERN. The implications of these findings are that those with mTBI/PTSD are less able to monitor their performance for errors. Prior results in TBI patients have included only those with severe injuries, and these studies have reported large ERN decreases (Larson et al., 2007; Swick & Turken, 2008). We will further examine this ERP measure in relation to scores on the BDI and PCS. Furthermore, we will analyze the relationship of ERN amplitude to performance adjustments after errors (e.g., posterror slowing).

KEY RESEARCH ACCOMPLISHMENTS:

- Enrolled 6 OEF/OIF Veterans with PTSD/mTBI and 12 Veteran control participants into the study.
- Continued recording ERPs for Exp. 2 and analyzing ERP data for Exp. 4.
- Discovered a significant reduction in ERN amplitude in OEF/OIF Veterans with mild TBI and PTSD, relative to the Veteran control group. This is a novel finding that has not been reported in the literature. Like many of the other measures in this project, there was a significant correlation between PCL-M scores and ERN amplitude.
- Saw a significant increase in the amplitude of the novelty P3a response in the patients with mTBI/PTSD, which replicated previous findings in PTSD (Kimble et al., 2000).
- Started to implement support vector machine learning algorithms in an effort to classify individuals as either having the disorder (PTSD alone or PTSD+mTBI) or as not having the disorder, based on EEG measures.
- Demonstrated that the emotional Stroop task with combat-related words is a robust and

sensitive measure of attentional bias to trauma-relevant material in OEF/OIF Veterans with PTSD. The addition of mTBI(s) did not compound this attentional bias effect. The emotional Stroop effect correlated quite strongly with the re-experiencing subscale of thee PCL-M.

- Found that OEF/OIF Veterans with PTSD exhibited an impulsive response style in a Go/NoGo task that measures the ability to inhibit inappropriate responses. The co-occurrence of mTBI and PTSD did not worsen the response inhibition deficit associated with PTSD alone. The severity of self-rated PTSD and depressive symptoms correlated with the degree of behavioral impairment on the task.
- Presented these behavioral findings as a slide presentation at last year's VA Research Day in Martinez, on April 28, 2010.
- Also presented these data at the VA/DoD Annual Conference at Travis Air Force Base/David Grant Medical Center (November 4, 2010).
- Published a paper comparing the neural correlates of two different response inhibition tasks, based on a meta-analysis of the neuroimaging literature. Clarifying the brain regions that implement performance of the Go/NoGo task will help identify the neural networks compromised in those with PTSD.
- Published a paper (pending revision) on how multitasking affects behavioral and neural measures of visual attention in control participants.
- Two publications on the response inhibition deficits associated with PTSD/mTBI are in preparation.

REPORTABLE OUTCOMES:

Abstracts

Ashley V, Swick D, Pratt N, Larsen J, Justus T. Attentional bias for trauma-related words: Exaggerated emotional Stroop effect in Iraq and Afghanistan war veterans with PTSD and TBI. Abstract submitted in Nov. 2010. Poster presented at the Cognitive Neuroscience Society Meeting, April 2011.

http://www.cnsmeeting.org/index.php?page=poster_detail&show=authors&sort=board_a&go=&id=48

Swick D, Ashley V, Turken AU. Performance on Go/NoGo and Stop-Signal response inhibition tasks is not correlated. Abstract submitted in Nov. 2010. Poster presented at the Cognitive Neuroscience Society Meeting, April 2011.

http://www.cnsmeeting.org/index.php?page=poster_detail&show=authors&sort=board_a&go=&id=458

Presentations

April 28, 2010: Featured speaker at VA Research Day in Martinez, gave a presentation on "Brain and Behavioral Changes in Veterans with PTSD and TBI: Towards Better Diagnosis and

Treatment." Members of my lab manned a booth explaining our research to other employees, veterans, and members of the public. These Research Day activities led to interviews and press coverage in *Contra Costa Times*: "VA medical center in Martinez a locus for research into traumatic brain injury" [no longer archived on website].

November 4, 2010: VA/DoD Annual Conference at Travis Air Force Base/David Grant Medical Center. The theme this year was "Behavioral Health Across the Continuum and the Generations." My presentation was on "Brain and Behavioral Changes in Veterans with PTSD and TBI: Towards Better Diagnosis and Treatment."

November 2010: Data from this project were presented by Dr. Anthony Chen at a DoD/TATRC meeting in San Francisco.

Feb 15, 2011: TBI Journal Club, Martinez VA

Publications

Swick D, Ashley V, Turken AU. (2011). Are the neural correlates of stopping and not going identical? Quantitative meta-analysis of two response inhibition tasks. *NeuroImage* 56: 1655-1665.

Pratt N, Willoughby A, Swick D. (in press). Effects of working memory load on visual selective attention: Behavioral and electrophysiological evidence. *Frontiers in Human Neuroscience*.

Swick D, Pratt N, Larsen J, Ashley V. (in preparation). Impaired response inhibition and cognitive control in veterans with post-traumatic stress disorder and mild traumatic brain injury.

<u>Related Publication</u> - This work was funded by the PI's VA Merit grant and is relevant to the present DoD project:

Justus, T., Larsen, J., Yang, J., de Mornay Davies, P., Dronkers, N., & Swick, D. (2011). The role of Broca's area in regular past-tense morphology: An event-related potential study. *Neuropsychologia* 49: 1-18.

CONCLUSIONS: Trauma-relevant words captured attention to a greater extent in Veterans with PTSD than in those without. Thus, the emotional Stroop test shows promise as an objective behavioral measure that may be able to distinguish between OEF/OIF combat Veterans with a PTSD diagnosis and those without. We believe it is a suitable test of emotional reactivity and attentional bias that can be obtained before and after behavioral and pharmacological therapies. In addition, the present group of patients showed a substantial deficit in motor response inhibition, which can have implications for daily life. Greater PTSD and depressive symptoms were both associated with worse performance on the task. However, performance on a different measure of response inhibition – the ability to suddenly stop an ongoing response based on a signal – was intact in the patients. The co-occurrence of mTBI and PTSD did not worsen the emotional and cognitive control difficulties associated with PTSD alone. Increased levels of impulsivity and a decreased ability to filter out distracting and emotionally intrusive information can negatively impact social and occupational functioning. In the future, computerized training

interventions that target emotional and cognitive control skills may assist these OEF/OIF veterans in returning to their previous levels of productivity. The carefully-designed computerized tasks implemented in this project accurately assess the cognitive and affective sequelae of mTBI and PTSD.

New EEG findings revealed that Veterans with mTBI/PTSD showed deficits in error monitoring processes that are implemented by the medial prefrontal cortex. In the future, support vector machine learning algorithms will be applied to sets of multiple EEG measures. This may assist in the classification of patient groups vs. controls.

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Ashley V, Swick D, Pratt N, Larsen J, Justus T. (2011). Attentional bias for trauma-related words: Exaggerated emotional Stroop effect in Iraq and Afghanistan war veterans with PTSD and TBI. Poster presented at the Cognitive Neuroscience Society Meeting, April 2011

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